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THE ROLE OF SPONTANEOUS ABORTION STUDIES IN ENVIRONMENTAL RESEARCH

by

Jennie Kline[1,2]
Zena Stein[1,2]
Maureen Hatch[1,2],
Barbara Strobino[1,2],

[1]Sergievsky Center
Columbia University
630 W. 168th Street
New York, New York 10032

and

[2]Epidemiology of Development Brain Disorders Department
New York State Psychiatric Institute
722 West 168th Street
New York, New York 10032

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Project Officer

R. Miday (July 1, 1980 - November 1, 1981)
G. F. Craun (November 1, 1981 - July 31, 1982)
Toxicology and Microbiology Division
Health Effects Research Laboratory
Cincinnati, Ohio 45268

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NORTH CAROLINA 27711

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16. ABSTRACT

The utility of studies of spontaneous abortion in detecting hazards to reproduction which arise in the work place or environment is assessed.

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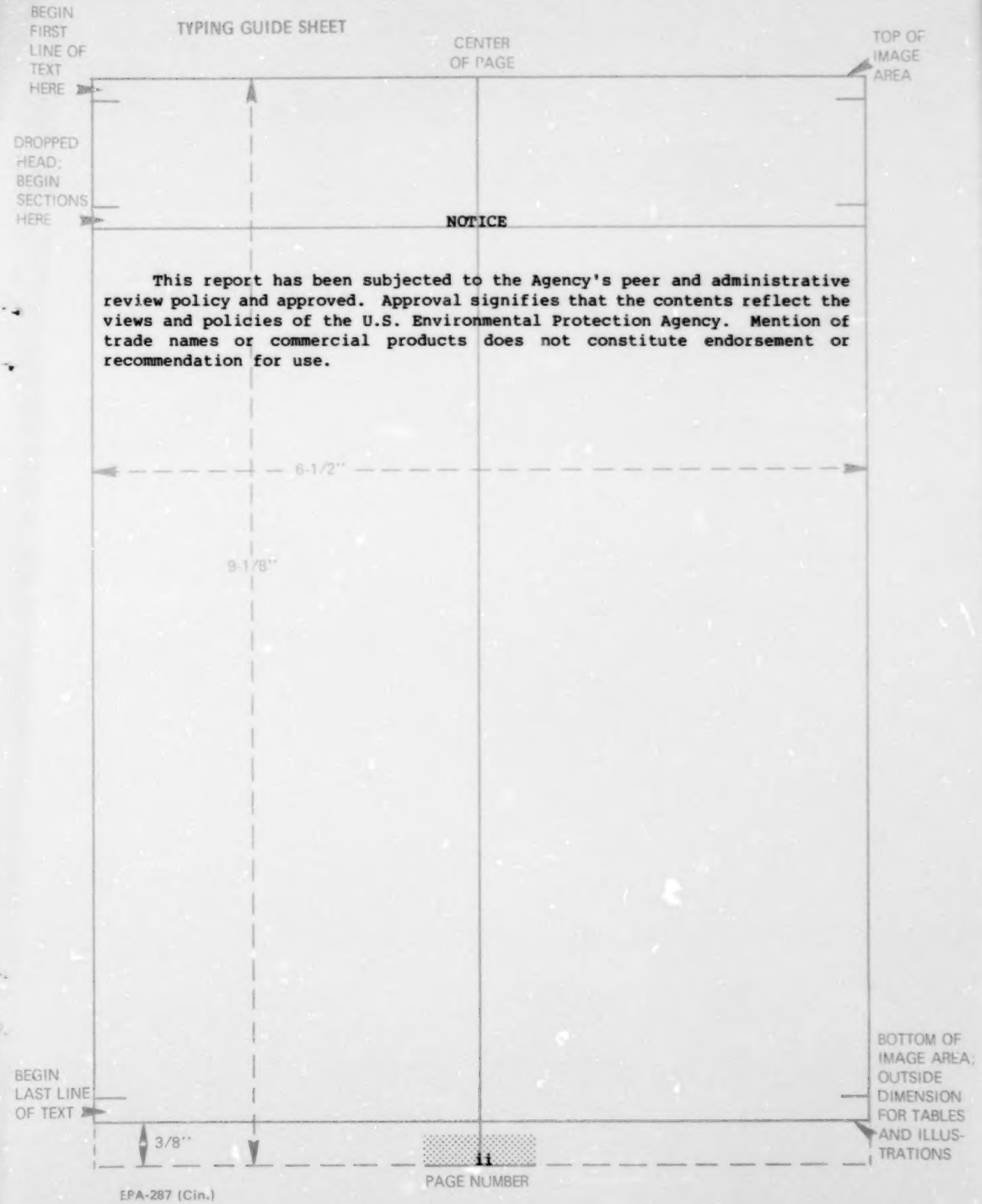
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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The complexities of environmental problems originate in the deep interdependent relationships between the various physical and biological segments of man's natural and social world. Solutions to these environmental problems require an integrated program of research and development using input from a number of disciplines. The Health Effects Research Laboratory, Research Triangle Park, NC and Cincinnati, OH, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. Wide ranges of pollutants known or suspected to cause health problems are studied. The research focuses on air pollutants, water pollutants, toxic substances, hazardous wastes, pesticides, and nonionizing radiation. The laboratory participates in the development and revision of air and water quality criteria and health assessment documents on pollutants for which regulatory actions are being considered. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of environmental regulatory decisions involving the protection of the health and welfare of all U.S. inhabitants.

Because of the recent interest in the use of spontaneous abortion as an endpoint for studies of environmental hazards to reproduction, we assessed the strengths and limitations of this outcome as an indicator of reproductive toxicity.

F. Gordon Hueter, Ph.D
Director
Health Effects Research Laboratory

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ABSTRACT

In this project we considered the utility of studies of spontaneous abortions to search for environmental exposures that may interfere with reproduction. The focus is on those exposures which usually have a low prevalence in the general population, such as exposures which may result from nearby chemical dumps or exposures which occur in the workplace.

Studies of spontaneous abortions offer the possibility of detecting agents which might have interfered with reproduction in a variety of ways. This is because spontaneous abortion is a heterogeneous outcome of pregnancy, comprising conceptions of different chromosomal and morphologic characteristics. In this report we review and evaluate the research stragegies which have been used to examine the relations of environmental exposures to spontaneous abortion. In most investigations a retrospective cohort design has been used in order to obtain sufficient numbers of exposed couples. This approach has the disadvantage that the chromosomal and morphologic characteristics of the abortus cannot be described. An overall increase in the rate of spontaneous abortion among exposed couples is most likely to reflect an increase in the rate of abortion for chromosomally normal conceptions, since these account for about two-thirds of abortions up to 28 weeks gestation. Excess abortions of this type most probably arise from maternal post-conceptional exposures, rather than pre-conceptional exposures to either parent.

The advantages and disadvantages of the retrospective cohort design and several other designs to the study of the relations of rare environmental exposures to spontaneous abortions and to fetal defects among abortions are considered. Methods of ascertaining spontaneous abortions are discussed in some detail.

This report was submitted in fulfillment of Cooperative Agreement R807355 by the Gertrude H. Sergievsky Center, Columbia University Health Sciences, under the sponsorship of the U.S. Environmental Protection Agency. This report covers a period from July 1, 1980, to January 31, 1982; work was completed as of January 31, 1982.

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V. Sources of Data on Spontaneous Abortion.

VI. Obstetric Records Survey Questionnaire.

VII. References for Published and/or Presented Papers resulting from this project.

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SECTION 1

INTRODUCTION

In this project, we considered the utility of studies of spontaneous abortions to search for environmental exposures which may interfere with the reproductive processes. We have focused on those environmental exposures which have a low prevalence in the general population, such as may result from nearby chemical dumps or industries, or exposures which occur in the workplace. Studies of the effects of more common environmental agents such as cigarettes or alcohol may serve as models for studies of rarer exposures, but certain methodological issues become particularly important when the exposure under consideration is rare.

In the three sections that follow, we outline the scope of the work and our conclusions. In the first section, we define spontaneous abortion and describe the heterogeneity of this outcome of pregnancy. The second section provides a brief overview of studies which have examined the relation of environmental exposures to spontaneous abortion. We append (Appendix I) a more detailed description of each of the studies reviewed in this section. In the third section, we consider methodologic issues relating to the study of spontaneous abortions, with emphasis on those issues which are particularly relevant to the study of rare exposures. This section draws heavily on our own experiences in considering research strategies for specific situations (e.g. environmental exposures to 2,4,5-T; Love Canal; occupational exposures in selected communities) and on our interviews with colleagues currently carrying out studies of specific occupational exposures. We append a table outlining the designs of each of these ongoing studies (Appendix II). In the fourth section, we summarize what might be learned from studies which relate environmental exposures to the rate of spontaneous abortion.

Over this project, we have published several papers dealing with the utility of using spontaneous abortions, and other reproductive outcomes, to identify environmental exposures which are hazardous to reproduction. This progress report serves as an outline to and summary of these papers. Each of the issues outlined in this report is discussed in greater detail in the papers, which are referenced in Appendix VII.

SPONTANEOUS ABORTION: FREQUENCY AND HETEROGENEITY

In developing the organizational form for the "Panel II Report: Guidelines for Reproductive Studies in Exposed Human Populations," we generated a list of possible endpoints that could be monitored or studied as part of an alerting system for a particular community or population. It was recognized that no one adverse reproductive endpoint could provide evidence regarding all possible reproductive effects of a suspect agent. As an obvious example, if infertility were to be the only effect of a

particular exposure (for instance, DBCP), there would be no conceptions, hence no spontaneous abortions. As another example, it is not at all certain that an exposure associated with low birthweight (like smoking) or malformations (like thalidomide) would necessarily also be associated with spontaneous abortion. Experimental teratologists have provided evidence that many exposures in laboratory animals are manifest only in one specific outcome. Thus a comprehensive evaluation of the possible reproductive effects of a suspect agent would require study of a range of outcomes.

Nevertheless, spontaneous abortion, defined as a nondeliberate termination of pregnancy up to the twenty-eighth week of gestation, is one of the more useful endpoints, for several reasons. One is statistical, relating to the frequency of spontaneous abortion, which occurs in about 15% of recognized pregnancies. Far fewer pregnancies need to be observed to detect a statistically significant excess in the incidence of spontaneous abortion than would be needed to show comparable excess in a less common outcome of pregnancy. For this reason, attempts to detect changes in the frequency of abortions may be more efficient and less time-consuming and expensive than studies of rarer endpoints.

A second reason relates to the fact that spontaneous abortion is in a sense not one homogeneous endpoint, but is the common outcome of several different processes. An inherited translocation in either parent, imperfect cleavage of the zygote, and a toxic exposure to the mother during pregnancy, for example, may each lead to an increased risk of abortion, but through different processes, acting at different times and on different targets. This heterogeneity adds to the usefulness of studying spontaneous abortions, especially if the abortus is examined cytogenetically. Thus one or a combination of several mechanisms linking an environmental exposure to adverse reproductive effects may be detected in a study which ascertains a sample of spontaneous abortions.

REVIEW OF THE LITERATURE

A variety of maternal environmental exposures has been examined in relation to the frequency of spontaneous abortion: these include irradiation, either from exposure to the atomic bomb or through medical care, occupational exposures to anesthesia, work in industries using chemicals, work in hospitals and laboratories, proximity to a lead smelter. In addition, studies carried out in Finland which link a computerized register of hospitalized spontaneous abortions and births to computerized employment data have provided an opportunity to screen a range of occupations; employment in chemical and metal industries and laundry and pharmaceutical companies showed positive associations in these exploratory analyses. The effects of anesthesia exposure on spontaneous abortion and other adverse pregnancy outcomes have been assessed in a number of studies; although the majority of studies report positive associations with spontaneous abortion, most of the research suffers from similar methodologic difficulties (e.g. low response rates, different response rates among exposed and unexposed women, inappropriate comparison groups, failure to separate the effects of pre-conception and post-conception exposure).

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Thus in spite of the several attempts to replicate the original observation, the association of this exposure with spontaneous abortion remains unclear. No other environmental or occupational exposure has been studied in so many different settings; for the most part, suspicions of adverse effects rest on a single observation. The assessment of the possible association of irradiation exposure with spontaneous abortion is unique in that two studies (Alberman et al 1972; Lazar et al 1973) have examined maternal exposure in relation to the chromosomal characteristics of the aborted conceptus. The findings of these two studies are conflicting; only the data from London (Alberman et al 1972) suggest an association, in this case a modest association between irradiation and triploidy. The reproductive effects of maternal occupational exposure to styrene and to pharmaceuticals are each currently being examined. In addition, exploratory analyses are underway of the occupations included among participants in the Collaborative Perinatal Project (Joyce Salg, NIOSH, personal communication, 1980) and among women participating in the New York City Pregnancy and Health Study (Kline et al 1978), and these may provide suggestions regarding occupational settings which carry exposures associated with malformation or with spontaneous abortion.

Paternal exposure to anesthesia has been examined on several occasions: as with the evidence on maternal exposure, the results of these studies are conflicting. The preponderance of studies of physicians suggest that paternal exposure is unassociated with an increased risk of spontaneous abortion, but two studies of dentists (Cohen et al 1975, 1980) raise the possibility that exposure to nitrous oxide, common in dental but not medical practice, may be associated with abortion. Many of the studies are plagued by low response rates and/or different response rates among exposed and unexposed men, and it may be that the reported positive and negative findings are spurious. A preliminary report from Israel has linked paternal DBCP exposure to spontaneous abortion (Kharrazi et al 1980). Paternal exposure to vinyl chloride (Infante et al 1976) has been examined in one study and another is close to completion. The associations of spontaneous abortion with paternal exposure to lead, carbon disulfide, toluene diamine/dinitrotoluene, and work in the rubber industry will be assessed in studies now underway.

Appendix I provides a description of studies in which the relations of environmental (including occupational) exposures to spontaneous abortions have been examined. This table includes a description of the study design, definitions of exposure, information on the source of data on both spontaneous abortion frequency and exposure, a summary of results, and a critique. In Appendix II we have similarly summarized the designs of ongoing studies; these data were obtained in interviews with the principal investigator and/or from presentations at meetings. Appendix III provides an updated bibliography (Strobino et al 1980) of studies in which the effect of environmental exposures such as smoking and prescription drugs, was assessed in relation to a range of reproductive outcomes.

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RESEARCH STRATEGIES IN SPONTANEOUS ABORTION STUDIES

Study Design

Several designs lend themselves to the investigation of the relation between an exposure and spontaneous abortion, depending on the circumstances.

Cohort studies: In situations where an adverse exposure has been suspected, it may be possible to secure and compare pregnancy histories for individuals living in exposed and unexposed areas, for the period of time in question. We have encountered three major problems in this type of study. First, since not all abortions reach hospitals, nor even physicians, nor are even clearly recognized by the women themselves, special attempts may be needed to secure comparable and valid counts, from one location to another. Second, even if the observer is satisfied that the counts have been obtained in a similar manner from the exposed and unexposed populations, individual risk factors (e.g. maternal age; smoking and alcohol drinking habits; previous spontaneous abortion) should be taken into consideration during the analysis. For some of these risk factors it may be possible to obtain retrospective histories by interview; for others (e.g. alcohol drinking) it is not clear that retrospective data will be accurate. We have also wrestled with a third problem which is whether multiple pregnancies occurring to a single couple may be counted (for the purposes of statistical analysis) as single independent events, or whether it is more rigorous, and more appropriate, to use a woman as the unit of analysis.

Case-Control studies: Another design is to compare the frequency of exposure among women experiencing abortions (cases) and controls, usually comprising women experiencing term births. Spontaneous abortions and control pregnancies may have occurred before the study is undertaken, or they may be ascertained as they occur, usually in a cross-sectional study. A design explored quite extensively by us was to identify spontaneous abortions at the time the woman sought care in a hospital. This approach, compared to studies based on abortions identified retrospectively, has the advantage that the abortus is available to the investigator for extensive examination. In such a hospital-based study, or alternatively in a prospective study, it is possible to utilize fully the advantages of the heterogeneity of outcomes included among spontaneous abortions. If the processes associated with abortions are to be fully studied, then the products of conception must be available for analysis.

We have attempted to mount this type of investigation in a hospital or group of hospitals serving communities in supposedly polluted environments or where a large portion of the population is employed in one industry. Technically, this plan seemed feasible, for the hospitals were willing to participate, and there seemed no reason to fear noncooperation by patient users. In practice, however, we were not able to find a location in which the numbers of exposed men and women justified setting in motion this type of design.

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In theory, different causes may operate, depending on whether a pregnancy failed soon after conception, or several weeks or months later. Thus chromosome anomalies incompatible with intrauterine survival, growth disorganized embryos, and amniotic sacs which contain no or slight evidence of embryonic development represent early termination of embryonal growth; chromosomally normal fetuses represent later terminations. Pathogenetic processes are seemingly quite distinctive.

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Length of gestation has sometimes been used as an indirect measure of the frequency of chromosomal or morphologic anomalies among spontaneous abortions. In practice, duration of gestation, as estimated from last menstrual period, captures these distinctions far more crudely than we would wish. In part, this may be due to inaccurate recall of gestation (especially after a lapse of some time), or to irregularities in the menstrual cycle of many women, in part it may reflect a lapse between the time of fetal death and expulsion of the conceptus; there is the impression that while some abortions occur shortly after cessation of embryonal growth, others occur after a period of retention which may extend over 6-7 weeks.

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In studies of abortions based on retrospective histories, this problem has not been fully resolved, save at one extreme of the distribution: abortions occurring after 20 weeks are rarely chromosomally abnormal. Prospective cohorts followed from the first missed period offer the hope that as more is understood of the symptoms and signs of early pregnancy, including endocrinological markers, duration of gestation at abortion will yield more precise information.

Sources of Data

On exposures: Appendix IV provides an annotated list of data sources which could be used to determine which agents are most likely to be encountered in particular work settings, and to identify locations where a large proportion of the population might be exposed to particular toxic substances, either through air, water or soil contamination or through occupation. Although exposure to many of the agents which are suspected of being hazardous to reproduction is rare in the general population, subgroups can be identified where exposure is more common, occurring in 10% or more of the population. In designing a study to examine the relation of a particular agent to spontaneous abortion, the data sources listed in Appendix IV might be used to identify subgroups where exposure is sufficiently common to explore an association with spontaneous abortion. A pilot study carried out to identify an area where the relation of 2,4,5-T exposure to spontaneous abortion might be examined (Hatch and Kline 1980) may be viewed as an outline of the steps which will usually need to be taken to identify a setting in which to evaluate a particular agent.

On spontaneous abortions: Appendix V provides a list of data sources which could be used to ascertain spontaneous abortions. We include here: fetal death certificates, although in most states only late fetal deaths may be ascertained through these records; hospital and physician records;

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interviews with women, men or both.

The completeness of ascertainment through hospital and physician records will vary depending on the types of records reviewed and the record-keeping systems of these facilities or physicians. For example, in three New York City hospitals, identification of spontaneous abortions requires the review of pathology records, the labor and delivery logs, the operating room schedule, the admission records to the emergency room, and patient charts on all floors serving obstetric and gynecology patients. At the outset of our study, we attempted to enumerate spontaneous abortions by review of a card system listing discharged obstetric patients, labor and delivery records for the previous year, pathology records for the previous year and fetal death certificates. The number of abortions identified in this manner ranged from 25-50% of those ascertained when the study was begun and abortions were identified daily. Thus, in this setting, an attempt to ascertain hospitalized spontaneous abortions retrospectively, through a review of available record systems, would result in a substantial underascertainment. It is not clear whether or not the abortions which would be identified in this manner are representative of all abortions occurring at the hospital. In our view, the underascertainment would be sufficiently large to cast doubt on the assumption that those identified were unbiased.

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Ascertainment of spontaneous abortions through medical records will not include episodes where medical attention was not sought. The frequency with which women seek medical attention, either by attending a physician or hospital, is little studied, although Taylor (1970) has examined the factors associated with timing of the first prenatal visit. In our New York City study we asked women seeking care at hospital for a spontaneous abortion (cases) and women seeking prenatal care by the twenty-second week of gestation and delivering at 28 weeks or later (controls) whether they had attended a hospital or physician for the care of a previous spontaneous abortion. In this series, the strongest determinant of whether medical attention was sought was gestation at the spontaneous abortion: among women experiencing spontaneous abortions in the pregnancy immediately prior to the study pregnancy, 58% of women experiencing abortions at twelve weeks or earlier, 81% of women experiencing abortions at 13-16 weeks and 84% of women experiencing abortions at 17-28 weeks had sought medical attention. We examined whether a number of maternal characteristics showed a consistent association with the frequency with which medical attention was sought across these three gestation groups. We considered: maternal age, status at entrance to our study (case or control), payment status (private or public patient at the study pregnancy), race (White, Black, Hispanic), gravidity at the study pregnancy (less than five, 5+), maternal education (less than high school, high school graduate, more than high school), number of previous spontaneous abortions (1, 2-10) and smoking history (never smoked, ex-smoker at the study pregnancy, smoker at the study pregnancy). None of these characteristics showed a consistent association with care-seeking behavior across the three gestational intervals, although among abortions occurring at 12 weeks or less, a greater proportion of nonsmokers than smokers had sought medical attention.

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Among women who seek medical attention for spontaneous abortion, the frequency of admission to hospital versus care on an outpatient basis will depend on the facilities in the area and on the obstetric practices of physicians. During our pilot study to identify a location in which the relation of 2,4,5-T to spontaneous abortion might be examined, we developed a questionnaire aimed at evaluating the utility of hospital and physician records to ascertain spontaneous abortions (Appendix VI). The questionnaire was administered to physicians and hospital personnel in urban and rural areas in two regions of the United States. This survey suggests that the rates of hospitalization for spontaneous abortion are variable; in one region approximately 14% of women who contacted a physician at the time of abortion were hospitalized, whereas in a second region 44% of women were hospitalized. Thus in both areas, ascertainment of medically-attended spontaneous abortions would need to draw not only on hospital records, but also on physician records of out-patient care.

Spontaneous abortions can also be ascertained through interview with women or their mates concerning previous pregnancies. This approach has been taken in nearly all of the studies to date on the relation of environmental and occupational exposures to spontaneous abortion. Selevan (1980) provides the only systematic asessment of whether the reports provided by men are similar to those provided by their wives. Her data indicate a close agreement between partners on the number of spontaneous abortions, but not on the timing and gestation of these abortions. Women respondents appeared to provide a more accurate description of the time at which the abortion occurred and the length of pregnancy at abortion. To our knowledge there have been no studies of the validity of interview data concerning spontaneous abortion (that is, an assessment of whether the report of events is indeed accurate), although our data and those of Selevan indicate that the reliability of interview data is high (that is, women will give similar histories at two interviews, separated in time).

Spontaneous abortions may also be ascertained prospectively in a sample identified at the diagnosis of pregnancy. In many settings, pregnancies ordinarily become known to medical facilities beginning two months after the last menstrual period; often a large proportion of pregnancies are not diagnosed until the middle of the second trimester (Kline and Stein 1982, in press). Prospective studies which draw on pregnancies diagnosed at medical facilities may therefore fail to include the majority of first trimester spontaneous abortions. Thus in most settings special studies will need to be mounted in order to identify women early enough in pregnancy to prospectively ascertain first trimester spontaneous abortions. The development of assays which permit the detection of low levels of human chorionic gonadotropin beginning around six weeks after the last menstrual period facilitates the diagnosis of pregnancy soon after conception. Two systematic attempts (Miller et al 1980; Kline et al 1981) have been made to study the frequency with which raised levels of hCG are followed by bleeding episodes in which it is not possible to confirm pregnancy by pathologic examination of the bleeding specimen. These studies are aimed at the identification of so-called "unrecognized" spontaneous abortions; these same tests can be used to study the frequency

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of early "recognized" spontaneous abortions (that is, abortions where confirmation of pregnancy is possible through pathologic examination). Although several investigators, ourselves included, have entertained the possibility of ascertaining spontaneous abortions prospectively by diagnosing pregnancy soon after conception in a cohort of women who are exposed to a suspect agent, the feasibility of this approach has yet to be tested. We have been unable to locate a setting in which the numbers of women exposed to a suspect agent is large enough to yield an adequate number of pregnancies to test whether the rate of spontaneous abortion is increased two-fold among exposed compared to unexposed women. In theory, a similar approach could be taken to explore the effects of exposure to the male partner, but in practice, the administration of pregnancy tests to their female partners might prove difficult because recruitment, testing and follow-up of female partners could not be based in one location.

Methodologic Problems Encountered in Ongoing Spontaneous Abortion Studies

The great majority of spontaneous abortion studies on environmental exposures, including those currently underway, have used a retrospective cohort design to examine the relation of exposure to the frequency of abortion. Typically the data on spontaneous abortions have been obtained through interviews, usually with the woman. The studies of Hemminki and colleagues in Finland are an exception to this approach; in these studies reproductive outcomes have been ascertained from a computerized register of hospital discharge diagnoses. Pregnancies recorded in this register were linked to occupational information via social security number, and the linked data were explored to identify occupations which appear to be associated with spontaneous abortion or other adverse pregnancy outcomes. The leads from this surveillance system can be followed up in special studies of the industry or occupation under suspicion.

For many of the exposures which have been or are being examined the retrospective cohort strategy is the only study design which can provide an adequate number of exposed pregnancies to search for modest effects on the risk of spontaneous abortion. As discussed above, this approach has the disadvantage that cytogenetic and morphologic descriptions of the abortus are not available. Modest associations between an exposure and spontaneous abortion in such studies are most likely to reflect an overall increase in the risk of chromosomally normal abortions (which occur in about two-thirds of all abortions); modest increases in the risk of chromosomal anomalies are unlikely to be detected in retrospective cohort studies (Kline 1982). In addition, the retrospective cohort study is usually time-consuming and expensive.

The research to date has emphasized workplace exposures over exposures to the community at large, in part because the exposure dose is presumed higher and in part because exposed individuals may be easier to identify in the occupational setting. Some investigators we spoke with noted that thus far, the selection of exposures for investigation has had to rest on weak evidence, consisting of a few suggestive observations in animals, occasional case reports or complaints from exposed individuals. The surveillance system in Finland and exploratory analyses of already

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collected data sets may serve in the future to guide investigators in the choice of suspect exposures.

In theory, the retrospective cohort approach may provide more detailed information on the characteristics and circumstances of exposure than a case-control study, since exposed and unexposed cohorts might be selected for study on the grounds that detailed records of exposure exist. In practice, retrospective cohort studies of spontaneous abortions have seldom realized this potential and this difficulty is owed in part to the fact that data from industrial hygiene surveys or environmental monitoring systems are relatively sparse.

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In many of the early retrospective cohort studies, information on the dependent variable consists only of a count of the number of spontaneous abortions. More recent studies, including those in the field, will attempt to obtain information on whether exposure occurred before and/or during each pregnancy, and on the gestation of pregnancy at abortion. This information may provide clues as to the likely mechanisms underlying an association of an exposure with spontaneous abortion.

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The major determinants of research strategy in these studies have been the low frequency of exposure to toxic agents (hence the cohort design) and the lack of routine data sources for spontaneous abortion (thus the use of interviews to ascertain outcome). Even with the cohort approach, however, the number of people exposed is small, hence the time frame must be extended to generate a sufficient number of events for study. The resulting lengthy period of recall about both reproductive and work histories is bound to introduce imprecision into the data, even where one is not worried about bias in participation or reporting. Moreover, the further back in time one goes, the less chance there is to confirm reported events in medical records since these are not retained indefinitely. Problems with follow-up are particularly severe in retrospective studies of exposed females, whose names may change with changes in marital status.

Some investigators have sensed confusion among respondents between induced and spontaneous abortions, although care in devising terminology for questionnaires and training interviewers should combat this problem. It may also be important to take the frequency of induced abortions into account in analyzing the results of spontaneous abortion studies. Differential rates of induced abortion among study groups may produce spurious findings. (The influence of induced abortion on rates of spontaneous abortion is discussed in the paper by Susser and Kline (1981) referenced in Appendix VII).

On the positive side, the experience to date suggests that the public is concerned with identifying the reproductive effects of environmental exposures and that both men and women are willing to discuss their reproductive histories in order to further this research.

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SECTION 2

CONCLUSIONS

Studies of spontaneous abortions to detect exposures which are hazardous to reproduction offer the possibility of detecting exposures which might have operated in a variety of ways. Thus exposures which interfere with embryogenesis, those which jeopardize the intrauterine survival of apparently normal conceptions and others, may be detected through a study of spontaneous abortions. Since about two-thirds of spontaneous abortions up to 28 weeks gestation are chromosomally normal, an overall increase in the frequency of spontaneous abortion is most likely to reflect an increase in the probability of this type of abortion. Although in theory an increase in the rate of spontaneous abortion might reflect an increase in the risk of a specific chromosomal anomaly (Kline et al 1977), a very large increase in the probability of anomaly at conception would need to underlie a detectable excess in the risk of spontaneous abortion in most populations.

In sum, given present knowledge, the major contribution of studies of spontaneous abortion rates would seem to be for post-conception maternal exposures, after the analogy of maternal smoking and alcohol ingestion.

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APPENDIX II: STUDIES OF SPONTANEOUS ABORTION AND ENVIRONMENTAL AGENTS
A. EXPOSURE TO THE MOTHER

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
K. Hemminki et al. Institute of Occupational Health, Helsinki, 1980	Maternal occupation and social class.	Retrospective cohort, 1973-1975. Exposed=6 social classes, 10 occupations. Reference group=all Finnish women.	1)Mother's occupation during pregnancy. 2)Socioeconomic status, based on broad occupational groupings defined by Finland's Central Statistical Office.	S.A.: ICD #643 and 645.	Parental occupation as reported in the Finnish National Board of Health's Hospital Discharge Registry	Hospital Discharge Registry	The frequency of (hospitalized) S.A. is increased among women in the lower social classes and in occupations involving physical and manual labor. Frequencies of SA were lower than average among housewives and women in clerical and managerial occupations.	-Despite a high rate of hospitalization for SA (~90%), the results could be biased if hospitalization varies by occupation or social class.
K. Hemminki et al. Institute of Occupational Health, Helsinki, 1980	Female workers in the metal industry.	Retrospective Cohort, 1973-76. Exposed=35,000 members of the metal workers union. Reference Groups: 1) All Finnish women 2) Union members prior to joining the union (i.e. pre-exposure).	Membership in the Union of Metal Workers prior to the hospitalization; by type of employment (e.g. electronics, shipbuilding).	S.A.: ICD #643 and 645.	Union membership rolls; supplemental data from the union industrial health staff on a subgroup of electronics workers.	Hospital Discharge Registry	S.A. ratio (SA/birth) but not S.A. rate (SA/preg) was increased for union members compared with all Finnish women. A higher rate of S.A. was noted for women in radio and TV section of the electronics branch. Both rate and ratio (age-standardized) were higher in union members after joining compared with before.	-Because induced abortion is frequent in Finland, SA ratio provides an overestimate and SA rate provides an underestimate of the true frequency. -The findings relate to preconception exposure and not to work status of the woman during pregnancy.

Key to Endpoint Abbreviations:

SA = spontaneous abortion
SB = stillbirth
BD = birth defects
BW = birthweight
LBW= low birthweight

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2. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
K. Hemminki, et al. Institute of Occupational Health, Helsinki 1980	Female chemical workers.	Retrospective cohort, 1973-76. Exposed=9000 members of the chemical workers union. Reference groups: 1) All Finnish women. 2) All women employed in industry and construction.	Membership in the Union of Chemical Workers prior to the hospitalization, by type of employment.	S.A.: ICD #643 and 645.	Union membership rolls.	Hospital Discharge Registry.	Both SA rate and ratio were raised in chemical workers compared with either reference group. Analysis by branch of employment found that plastics workers and women in the viscose rayon industry were at highest risk. The ratio of S.A. was also raised among laundry and pharmaceutical workers.	-These findings relate to preconception exposure and not to work status of the woman during pregnancy.
S. Nordstrom et al. U. of Umea, Sweden 1979	Female workers at a lead/arsenic smelter.	Retrospective cohort, women workers born 1930 - 59; N=511 Exposed = women employed at the smelter during pregnancy; previous employees living < 10 km. from the smelter during pregnancy. Unexposed women employed either pre or post-pregnancy, and living > 10 km. from the smelter.	Working at the smelter during pregnancy; job category used to indicate level of exposure.	S.A., B.W.	Company personnel records.	Mailed questionnaire -83% response rate; and hospital records.	Higher rates of SA were observed in women working at the smelter during pregnancy, and in previous employees living close to the smelter. The highest rates were observed in women working in smelting/cleaning operations.	-Parity, but not maternal age was controlled in the analysis. -Effects were concentrated in later pregnancies. -Excess risk was further increased if father also worked at the smelter.

3). Exposure to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Birgitta Kolmodin-Hedman, et al. University Hospital, Uppsala 1981	1) Women workers in the steel industry. 2) Women working in pharmaceutical laboratories.	Retrospective cohort: 1)Exposed=461 female industrial workers at a steel plant. Unexposed= 132 clerical workers at a steel plant. 2) Exposed=238 lab workers Unexposed=236 clerical workers at a pharmaceutical plant.	Job title/ location during pregnancy: 1) steel worker 2) lab worker	SA, BD	Maternal report of job history at personal interview.	Interview	No difference in rates of SA between either group of exposed women and their unexposed comparison group.	-Each job entails multiple exposures. -The data suggest a slight increase in SA rate in steel workers which may be explained by smoking.
Lene Zeuthen Heidam U. of Odense, Denmark 1981	Maternal occupations involving exposure to chemicals.	Retrospective cohort: N=6700. Exposed = factory workers, lab workers, painters, gardeners, dental assistants. Unexposed = office workers, supermarket workers, technical artists, shop assistants.	Specific occupation for ≥ 1 mo. duration during pregnancy; exposure to specific substances.	SA, premature delivery.	Mailed questionnaire to women identified through company or union files.	Questionnaire	SA rate significantly higher in factory than supermarket workers; within factory workers there is a trend to higher rates in those reporting chemical exposure v. those who report they are not exposed.	-Telephone follow-up yielded a final response rate of 90%; nonresponse was the highest among women with little education. -Previous obstetric history, a potentially confounding factor, was controlled in these analyses.

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4. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Evert Hansson et al, U. of Lund, Sweden 1980	Female lab workers in three pharmaceutical companies.	Retrospective cohort analysis. Exposed = 110 lab workers Unexposed = 625 women working in other areas of the company.	? Ever employed as a lab worker.	S.A.	Company records.	Either interview, mailed questionnaire or computerized register of deliveries, depending on the study site.	SA rate was higher in the laboratory workers (18%) than in the non-laboratory workers (10%).	-Although age was not controlled in the analysis, the exposed group was younger, which would underestimate the effect. -Methods of data collection were not uniform throughout the three study sites.
May Strandberg et al, Central Hospital Karlstad, Sweden 1978	Currently employed female workers in a hospital laboratory.	Pre/Post exposure comparison of pregnancy outcome in 56 current laboratory workers.	Exposed = lab work during the pregnancy	S.A.	Interview	Interview	On a one-tailed test, the risk of SA is raised among exposed versus unexposed pregnancies (risk ratio ≃ 1.7).	-Sample size is very small: 24 exposed versus 47 unexposed pregnancies. -Covariates were analyzed using a multivariate confounder score.
Nader Kavoussi U. of Teheran, Iran 1977	Female textile workers.	Retrospective cohort analysis. Exposed = 272 married female textile workers, ≥ 30. Unexposed = 217 non-working wives of male textile workers; wives were also ≥ 30.	? Ever worked in textile factory.	S.A.	Personal interview.	Interview with the wives.	Rate of SA similar in working women and nonworking wives (11% v. 9%).	-No formal significance tests were applied. -Age at interview was considered in the analysis, but not age at pregnancy.

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5. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Ellis Cohen et al Stanford Univ. 1971	Female operating room (OR) nurses and anesthesiologists.	Retrospective cohort study. (1) Exposed= 67 OR nurses; Unexposed=92 general duty nurses. (2) Exposed = 50 anesthesiologists Unexposed = 81 MD's in other specialties.	Work in the OR at any time during the 5-year study period.	S.A.	Personal interview (nurses). Questionnaire (physicians).	Personal interview (nurses). Questionnaire (physicians).	An increased rate of SA was observed among both exposed nurses (30% v 9%) and exposed physicians (38% v 10%). SA among exposed pregnancies occurred on average two weeks earlier in gestation.	-Pre and post-conception exposure are not distinguished. -Maternal age is not controlled and both exposed cohorts are older on average than their comparison groups. -The number of pregnancies available for analysis are few (N= 165).
Ad Hoc Committee on Anesthetic Agents, Amer. Soc. of Anesthesiologists 1974	Female (and male) operating room personnel.	Retrospective cohort study. (1)Exposed ≃ 10,000 pregnancies to anesthesiologists, nurse anesthetists, OR nurses and technicians; unexposed = 3000 pregnancies to pediatricians + non-OR nurses. (2)Internal comparison of exposed and unexposed pregnancies among OR personnel.	Work in the OR in the year prior to conception and during the first trimester of pregnancy.	S.A., B.D.	Mailed questionnaire to members of professional societies	Mailed questionnaire	-SA rates are higher in anesthesiologists (17%)than in pediatricians (8.9%), and in OR nurses (17%) compared with non-OR nurses (15%). SA rates in unexposed pregnancies of anesthesiologists were close to the rate in exposed pregnancies (15.7 v. 17.1%).	-Low and unequal response rates in exposed (60%) and unexposed (42%)nurses; rates for physicians were almost equivalent (76% v. 73%). -Definition cannot distinguish pre-and post-conception exposures. -SA rates for anesthesiologists were not not comparable to pediatricians, even in unexposed pregnancies.

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6. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
R.P. Knill-Jones et al. U. of Glasgow 1972	Female anesthesiologists	Retrospective cohort analysis. Exposed=563 anesthesiologists; Unexposed = 828 physicians in other specialties.	OR work in the first or second trimester of pregnancy.	SA, SB, neonatal deaths, BD, sex ratio, infertility.	Mailed questionnaires	Mailed questionnaires	SA rates were significantly increased in exposed pregnancies (18.2% v. 14.7% in controls), as were rates of infertility (12% v. 6%).	-Response rates are equivalent in exposed (82%) and unexposed (80%). -SA rate in unexposed pregnancies is similar to controls. -Exposed women were younger so the effect may be underestimated.
P.O.D. Pharoah et al, London School of Hygiene 1977	Female anesthesiologists.	Retrospective cohort analysis. Exposed ≃ 670 pregnancies to anesthesiologists. Unexposed ≃ 8400 unexposed pregnancies to women with other medical appointments' or physicians who did not work during pregnancy	Medical appointment in anesthesia at the time of conception	SA, SB, BW, BD	Mailed questionnaire	Mailed questionnaire	SA rates did not differ between anesthesiologists and women with other appointments; rate in women not working at conception was significantly lower. -Exposed pregnancies resulted in lower birthweight ($p<.01$), a significant excess of malformations of the heart and great vessels, and a non-significant increase in stillbirths.	-Overall response rate was 72%; rate for exposed and unexposed not given.
A.Ericson et al. National Board of Health, Sweden, 1979	Female operating room personnel.	Retrospective cohort analysis. Exposed = 494 women working in ORs; Unexposed = other medical personnel delivering during the 2-yr. study period.	OR work throughout pregnancy.	"Threatened abortion", BW, perinatal deaths, BD.	Register of Swedish health care workers; verification at place of work.	Register of all deliveries.	No differences in threatened abortion, BW, BD or perinatal deaths; a small increase in pre-term delivery among OR personnel.	-Use of record-based data eliminates the potential for bias in recall of exposed and unexposed individuals.

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7. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
P.H. Rosenberg et al, Helsinki University, 1973	Female operating room nurses.	Retrospective cohort analysis Exposed=58 nurse anesthetists and 124 scrub nurses; Unexposed=75 casualty department nurses and 43 intensive care unit nurses.	OR work during pregnancy.	SA, LBW, menstrual problems.	Mailed questionnaire	Mailed questionnaire	SA rates during employment were higher among OR nurses (anesthetists = 15%, scrub nurses = 21.5%; total OR = 19.5%) then non-OR nurses (casualty = 8%, ICU = 16.7%; total non-OR = 11.4%).	-Nurse anesthetists had higher SA rates prior to employment than did the other categories of nurses. -X-ray exposure was also higher in OR v non-OR nurses. -Response rates were 70-75% in each category.
P.H. Rosenberg et al, Helsinki University, 1978	Female (and male) anesthesiologists.	Retrospective cohort analysis. Exposed = 180 male & female anesthesiologists Unexposed = 228 male & female pediatricians.	OR work at any time during the study period	S.A., B.D.	Mailed questionnaires to members of professional societies.	Mailed questionnaires	SA occurred less frequently in the families of anesthesiologists than of pediatricians. Gestation at delivery was two weeks earlier on average in the anesthetic group. An excess of musculoskeletal defects was observed in anesthesiologists' offspring.	-Does not successfully distinguish maternal and paternal exposure. -Response rates differ in exposed (85%) and unexposed (64%).
P.J. Tomlin, Queen Elizabeth Hospital, Birmingham 1979	Female (and male) anesthesiologists	Retrospective pre/post-exposure comparison. Exposed ~ 32 pregnancies; Unexposed = 102 pregnancies.	OR work during the year preceding conception	SA, BW "non-acquired" defects, childhood cancer.	Mailed questionnaire	Mailed questionnaire	SA rate was significantly raised among pregnancies to exposed mothers; BW, non-acquired defects and cancer in offspring similar in exposed and unexposed pregnancies.	-Analysis based on very small sample of pregnancies. -Response rate among females = 92%. -Maternal age was not controlled for in a before/after comparison spanning 20 years.

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8. Exposures to the Mother (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
P.J. Tomlin, Queen Elizabeth Hospital, Birmingham (continued)								-Definition of defects included anomalies which may be postnatal in origin.
Ellis Cohen et al, Stanford U, 1980	Female (and male) dental personnel	Retrospective cohort analysis. Exposed = 800 pregnancies to dental assistants using inhalation anesthetics; Unexposed $\simeq$ 3200 pregnancies to assistants of nonuser dentists	At least 1/hr week exposure during the year prior to conception. Light exposure; 1-8 hrs/wk. Heavy exposure: >8 hrs/ week	SA = fetal loss < 20 wks gestation; BD	Mailed questionnaire (names provided by participating dentists.	Mailed questionnaire	RR = 1.7-2.3 for SA among exposed v. unexposed dental assistants. Incidence of birth defects also significantly increased. Risk for both outcomes is higher in the group exposed to N_2O plus other agents than in those exposed to N_2O alone.	-Dose response relation for SA but not congenital defects. -Nature of the exposure is better specified than in earlier studies of anesthetic agents. -Definition does not distinguish pre- and post-conception exposure. -Overall response rate among dental assistants was 70%.
R.P. Knill-Jones et al, U. of Glasgow 1981	Females anesthesiologists.	Prospective follow-up of 6540 women physicians as they begin junior hospital appointments.	Working in anesthesia during pregnancy	SA, BD, BW	Mailed questionnaire	Mailed questionnaire	No significant increase in SA rates in doctors in anesthesia (12.4%) compared with other hospital doctors (10.4%); no difference in abnormality rates. A small effect on mean birthweight was observed: women not working (3380g); women in anesthesia (3310g); women in other specialties (3330g).	-Response rates to initial mailings, 78-84%, and to annual follow-ups, 93-98%. -Analysis is based on pregnancies ascertained retrospectively as well as prospectively.

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B. Exposure to the Father

Researcher and Affiliation	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Peter F. Infante et al, NIOSH 1976	Male workers exposed to vinyl chloride monomer (VCM).	Retrospective cohort. Exposed-95 polymerization workers. Unexposed - 158 rubber and fabrication workers, matched to exposed on age.	Job categories involving exposure to vinyl chloride monomer.	Fatal death: "any product of conception not born alive."	Company records	Interviews with the father.	Age-adjusted fetal death rates were higher in the group with VCM exposure, compared with controls.	The significant excess is reduced to a nonsignificant trend when women with 2 or more SA in the pre-exposure period are removed from the analysis.
Martin Kharrazi et al Ben-Gurion University Israel 1980	Male banana workers exposed to DBCP	Pre-Post Exposure comparison of pregnancy outcome. Post-exposure - 121 pregnancies; pre-exposure - 76 pregnancies	Direct contact with DBCP as field applicator, for at least one spraying season.	S.A.	Kibbutz records.	Interviews with the father and hospital records where available.	Pre-exposure rate of SA - 6.6%; post-exposure rate - 19.8%. In a subsample of 16 couples with pregnancies in both periods, pre-exposure rate - 5.9%; post-exposure rate - 27.5%.	"Though maternal age was not controlled in the analysis, the difference in mean age in the pre-post exposure period is not sufficient to account for the finding.

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10. Exposures to the Father (continued)

Researcher and Affiliation	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Ad Hoc Committee on Anesthetic Agents, American Society of Anesthesiologists 1974	Male (and female) operating room personnel	Retrospective cohort-analysis. Exposed ≃ 8000 pregnancies to wives of anesthesiologists, nurse anesthetists, OR nurses and technicians. Unexposed ≃ 2600 pregnancies to wives of pediatricians and non-OR nurses.	Work in the OR in the year prior to conception.	SA, BD	Mailed questionnaire to members of professional societies	Mailed questionnaire	No increased risk of SA in wives of exposed v. unexposed males; a small increase was observed in the incidence of congenital defects in offspring of exposed men.	-Low and unequal response rates in exposed (60%) and unexposed (40%). -No data on agent or exposure dose.
R.P. Knill-Jones et al U. of Glasgow 1975	Male anesthesiologists and surgeons	Retrospective cohort analysis. Exposed = anesthesiologists and surgeons (~6000 pregnancies). Unexposed = physicians in other specialties (~7300 pregnancies)	Work in the OR in the first trimester of the wife's pregnancy.	SA, BD infertility.	Mailed questionnaire	Mailed questionnaire	No increase in rates of SA, major malformations or infertility. A small increase (3.1% v. 2.4%) was observed in minor anomalies among offspring of exposed fathers.	-Overall response rate 70%; rate for exposed and unexposed not given. -Minor defects are subject to reporting bias.
Ellis Cohen et al Stanford U 1975	Male oral surgeons and dentists.	Retrospective cohort analysis. Exposed = 887 users of inhalation anesthetics. Unexposed = 1541 nonusers.	At least 3/hr wk. exposure during the year prior to conception	SA = fetal loss <20 wks gestation; BD	Mailed questionnaire	Mailed questionnaire	Significant increase in SA rate in wives of exposed (16%) v. unexposed (9%). No significant increase in birth defects, with exposure.	-Low and unequal response rate in exposed (65%) and unexposed (39%).

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II. Exposures to the Father (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
P.J. Tomlin Queen Elizabeth Hospital, Birmingham 1979	Male (and female) anesthesiologists	Retrospective pre-post-exposure comparison. Exposed ≃ 280 pregnancies. Unexposed = 102 pregnancies.	OR work during the year preceding conception. Unexposed = prior to OR work or ≥ 1 year after leaving OR.	SA, BW, "non-acquired" defects	Mailed questionnaire	Mailed questionnaire	No significant increase in rate of SA associated with paternal exposure. A non-significant increase in congenital defects was observed in offspring of exposed fathers.	-Overall response rate was 92%. -Maternal age was not controlled for in a before/after comparison spanning 20 years. -Defects included anomalies which may arise postnatally.
Ellis Cohen et al, Stanford U, 1980	Male (plus female) dental personnel.	Retrospective cohort analysis. Exposed ≃ 3400 pregnancies to users of inhalation anesthetics (chiefly N_2O); unexposed = 5700 nonusers.	At least 1 hr/wk exposure during the year prior to conception. Light exposure: 1-8 hrs/week Heavy exposure: >8 hrs/week	SA = fetal loss<20 weeks gestation; BD	Mailed questionnaires to professional society.	Mailed questionnaire	Increase of 50% in SA rate among wives of users v. nonusers. No increase in incidence of defects in offspring of exposed fathers.	-Dose-response effect observed. -Equivalent response rates in the groups originallyidentified as users (74.7%) and nonusers (72.1%) but among the respondents 60% are true users and 40% are true nonusers.

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C. Community Exposure

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
S. Nordstrom et al U. of Umea, Sweden 1978	Community surrounding a lead/arsenic smelter	Retrospective cohort analysis of all pregnancies to women born ≥ 1930, and living in one of four areas located at increasing distances from the smelter.	Proximity to smelter at time of delivery - Area A: "few" Area B: <10 km Area C: >10 km Area D: distant	S.A.	Umea Hospital records	Umea Hospital records	Significant increase in SA rate in Area A (11%) v. Area D (7.6%). There was an excess in Area A, compared with all other areas of women with "only abortions and no normal pregnancies."	-Parity, but not maternal age, is controlled in these analyses. -Analysis does not exclude residents who also work at the smelter. -Distance showed a dose-response relation.
Nicholas J. Vianna NYS Dept. of Health 1980	Community surrounding the Love Canal chemical dump site	Retrospective cohort analysis. Exposed = resident of study area. External reference group: Canadian series of 6000 pregnancies ascertained in a medical genetics unit. Internal comparison group: residents in non-water area.	Residence during pregnancy as indicator of exposure dose: (1) Adjacent to the canal. (2) "water house" (ie, transected by a potential route of chemical migration). (3) "non-water house."	SA, LBW	Place of residence	Interviews with residents; 98% participation Data on BW were confirmed in birth certificates.	No significant excess of SA (or LBW) in Love Canal as a whole or streets adjacent to the Canal, but rates in the water area were significantly increased compared to either the external or internal reference groups.	-Recall bias is a potential threat to the findings in SA and BD, but not to the data on BW. -The external reference group is not a comparable population.

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13. Community Exposure (continued)

Researcher and Affiliated Institution	Exposure and Population Studied	Study Design	Definition of		Sources of Data on:		Results	Comments
			Exposure	Endpoint	Exposure	Endpoint		
Epidemiology Studies Division, U.S. Environmental Protection Agency 1979	Residents of areas sprayed aerially with the herbicide 2,4,5-T	Ecologic analysis of SA ratios (SA/LB) in three areas of Oregon, 1972-1977. Exposed - forested region of Oregon's Coastal Range. Unexposed - 1. rural area where aerial spraying is not practiced 2. urban area adjacent to the study area	Residence in an area subject to aerial spraying with 2,4,5-T.	SA; ICD # 643.0-.3, 643.9, 644	Records of herbicide applications in a portion (25%) of the study area.	Hospital records.	The ratio of hospitalized SA to Live-births was significantly higher in the study area than in either of the two control areas. With-in the study areas there was a significant correlation between monthly amounts of herbicide applied and the monthly spontaneous abortion ratio.	-Rates of hospitalization for spontaneous abortion were not comparable in the study and unexposed areas. -The pattern of herbicide use upon which the correlation analysis is based was extrapolated from data on 1/4 of the study area.
E. Reuberger et al Givaudan Research Co. & Hoffmann - LaRoche Co. 1979	Population in the vicinity of an accidental release of TCDD (dioxin) from a plant in Seveso, Italy	Prospective follow-up of residents of contaminated and non-contaminated areas. Reference groups - townships outside contaminated areas.	Area zoned according to level of TCDD detected in soil samples: Zone A:[illegible] Zone B:[illegible] Zone R:<5 [illegible]	SA	Environmental sampling	?	Unclear	-The data are difficult to interpret, owing in part to the loss to follow-up of pregnancies terminated in unreported induced abortions

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APPENDIX II: ONGOING STUDIES OF SPONTANEOUS ABORTIONS

Researcher and Affiliated Institution	Exposure Population Studied	Study Design	Definition of: Exposure	Endpoint	Sources of data on: Exposure	Sources of data on: Endpoint	Response Rate	Comments
Grace LeMasters, U. of Cincinnati **(EPA Sponsored)**	Styrene exposure in female workers	Retrospective cohort: (1:1); N=2000. Exposed=1000 female laminators from different plastics firms; chiefly boat-companies. Unexposed = 1000 female assembly operators from same company or workers from manufacturing company in the same community.	Maternal exposure during pregnancy. For workers in boat companies: Direct contact: 50-150 ppm Indirect contact: 12 - 30 ppm. For workers in other plastics companies: < 30 ppm (Estimates of exposure levels based on industrial hygiene data.)	Pregnancy outcome: SA, BW, sex ratio, gestation, complications of pregnancy, major malformations	Maternal recall of work history (job titles) at phone interview	Telephone interview	90%	-Validation of sub-sample in medical records and company personnel records. -Planning reliability test/ retest on 5% of sample. -Work history taken after reproductive history to blind interviewer. -High turnover rate of workers makes recall of job title during pregnancy difficult, raising the possibility of misclassification of exposure status.
Sherry G. Selevan NIOSH	Carbon disulfide exposure to male textile workers.	Retrospective cohort: 1.5:1, N=500, Exposed: 200 male viscose rayon plant workers from exposed departments. Unexposed =300 male workers from unexposed areas in same plant.	Paternal exposure 3 months prior to conception, measured by ambient air levels in department: High: > 7 ppm Mod.: 3-7 ppm Low: < 3 ppm Other: unknown level	Pregnancy Outcome: (SA ≤ 20 wks); late fetal loss (>20 wks); LBW.	Ambient air measures by department; average of 6 mo. prior and 2 mo. post conception	Telephone interview with workers' wives.	88%	-Birth certificate validation. -Reliability test/retest on a 40% sample.

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APPENDIX II: ONGOING STUDIES OF SPONTANEOUS ABORTIONS

Researcher and Affiliated Institution	Exposure Population Studied	Study Design	Definition of: Exposure	Endpoint	Sources of data on: Exposure	Sources of data on: Endpoint	Response Rate	Comments
Cindy Robinson NIOSH	Exposures to pharmaceuticals in female laboratory workers.	Retrospective cohort: (1:3), N = 800. Exposed = 200 female lab workers. Unexposed = 600 female office workers at same facility.	Maternal exposure prior to or during pregnancy, defined as having worked in lab. building more than six months during 1968-1977. No air sampling measurements.	Pregnancy outcome: SA, SB, Ind. Ab., BD, morbidity in offspring.	Company personnel records.	Telephone interview	94.5%	-Possible birth certificate validation. -Planning reliability test/retest on 25% of sample. -Exposure very broadly defined: pharmaceuticals rather than specific compounds.
Sherry G. Selevan NIOSH	Lead exposures to male workers.	Retrospective cohort: N=395 workers at a lead battery plant.	Paternal blood lead levels at peri-fertilization; ranging from low to high: 29 mg – 70-80 mg	Pregnancy outcome: SA (≤ 20 wks gest.); late fetal loss (>20 wks gest); LBW.	Average of blood lead levels from 6 mo. prior to 2 mo. post conception	Interview with workers' wives.	70%	-Validation of sub-sample in medical records. -Biological measure of exposure. -No unexposed comparison group, but pre-employment pregnancies of the lead workers will be analyzed.

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Researcher and Affiliated Institution	Exposure Population Studied	Study Design	Definition of: Exposure	Endpoint	Sources of data on: Exposure	Sources of data on: Endpoint	Response Rate	Comments
Channing Meyer Univ. of Cincinnati	Carbon disulfide exposure to male textile workers.	Cross-sectional: (1:1), N=220 of 500 eligible viscose rayon plant workers. Exposed = workers from exposed departments. Unexposed = workers from unexposed areas in same plant.	Paternal exposure at peri-fertilization, measured by ambient air levels in departments. High: 30-60 mg/M^3 Moderate: 6-30 mg/M^3 Low: <6 mg/M^3 Other: level unknown.	Semen quality including: count morphology	Ambient air measures by department: average of levels 6 mo prior and 2 mo. post conception	Physician exam: lab data.	51% overall	-Substudy of NIOSH carbon disulfide research. No arrangement for linking data on male worker's semen quality with NIOSH findings on their wives' reproductive histories.
Channing Meyer, Univ. of Cincinnati & Steven Ahrenholz, Hazard Evaluations and Technical Assistance Branch, NIOSH	Toluene diamine and dinitrotoluene exposure to male chemical workers.	Retrospective/cross-sectional: N=30 chemical workers in 3 exposure categories.	Paternal exposure: High: present exposure to TDA/DNT on daily basis. Intermediate: past intermittent exposure to TDA/DNT with no contact during 2 years previous to study. Unexposed: no known exposure.	Semen quality: count morphology. Pregnancy outcome: SA,BD.	Company records, with personal and area air monitoring to indicate exposure levels.	Questionnaire to wives; lab data on semen.	64% participation rate in all three exposure categories.	-N is very small.

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APPENDIX II: ONGOING STUDIES OF SPONTANEOUS ABORTIONS

Researcher and Affiliated Institution	Exposure Population Studied	Study Design	Definition of: Exposure	Endpoint	Sources of data on: Exposure	Sources of data on: Endpoint	Response Rate	Comments
Richard Monson, Harvard University	Male exposure to rubber work.	Case-Control; N ≈ 24,000. Case=pregnancy complications and adverse outcomes (all cases occurring 1969-76). Control= a 10% -20% sample of normal live births occurring between 1969-1976.	Exposure defined as whether patient's husband was or was not a rubber worker at time of hospitalization of h[illegible] wife.	Pregnancy outcomes; SA,SB,BD, complications of pregnancy.	Hospital record (perhaps supplemented by company data).	Hospital record.	--	-Spouse employer on hospital record may be an imprecise source of exposure data; timing of exposure in relation to the pregnancy is also unclear.
Patricia Buffler, University of Texas	Male vinyl chloride workers.	Retrospective cohort: N=450. Exposed=248 vinyl chloride workers. Unexposed=202 company employees with no history of chemical exposure, matched on skill level.	"Documented" paternal vinyl chloride (VC) exposure of ≥ 3 months duration immediately prior to conception.	Delay in conception, SA,SB,BD.	Company records of job assignments; jobs have been ranked according to level of exposure to VC at different points during the study period.	Telephone interview with workers' wives.	82.7% in exposed; 71.3% in unexposed.	-Interviewers were blind to status of the study subjects and to the study's hypothesis. -Reports of late fetal loss (>20 wks gestation) were validated in vital records; birth certificate validation is planned. -The recall period is very long (up to 28 years).

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APPENDIX III

BIBLIOGRAPHY OF RESEARCH ON ENVIRONMENTAL AGENTS AND HUMAN REPRODUCTIVE OUTCOMES

The following bibliography is an updated version of one originally appearing in an article by Strobino, Kline and Stein (J Early Hum Devel 1:371-399, 1978). It is a selected bibliography in that special attention is given to original and early reports, and also to recent reports. An effort was made to include all population studies: case reports were included if they were numerous, or where the effects seemed highly specific in relation to a particular agent. The updated bibliography is reproduced from "Report of Panel II: Guidelines for Reproductive Studies in Exposed Populations," in Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards, Arthur D. Bloom, ed., March of Dimes Birth Defects Foundation, 1981.

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APPENDIX IV

SOURCES OF DATA ON ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

I. DATA FOR IDENTIFYING TOXIC SUBSTANCES:

1. NIOSH: RTECS (Registry of Toxic Effects of Chemical Substances). List of substances which have been implicated as carcinogens, mutagens or teratogens. Chemical Abstract Service Registry number, toxic dose data, and existing Federal standards are among the data provided for each chemical.

2. NIOSH: STANDARD CHEMICAL COMPLETION PROGRAM - Literatures review which provides background information on particular chemicals and their effects.

3. NIOSH-OSHA Pocket Guide to Chemical Hazards, publication No. 78-210.

4. KIRK-OTHMER ENCYCLOPEDIA OF CHEMICAL TECHNOLOGY: This encyclopedia can be used to find the physical properties of a chemical, its reactions with other compounds, its uses, methods of production, toxicity data (which include maximum allowable exposure) and health and safety factors. The index has a listing of chemical names, chemical group names, reactions, and range of topics such as industrial hygiene.

5. THE MERCK INDEX: AN ENCYCLOPEDIA OF CHEMICALS AND DRUGS: Toxicity data are given in this reference book listing chemicals and their properties.

6. DANGEROUS PROPERTIES OF INDUSTRIAL MATERIALS, N. Irving Sax (Van Nostrand Rheinhold Co., N.Y. 1975, 4th Ed.): A source of concise hazard analysis data about approximately 13,000 common industrial and laboratory materials. A toxic hazard rating or toxicology paragraph is given, as is a disaster hazard rating. Countermeasures which may be used to protect against the effects of a given material are also included.

7. CHEMICAL HAZARDS OF THE WORKPLACE: Nick Proctor and James P. Hughes (J.B. Lippincott Co., Philadelphia): Provides information on health risks of various chemicals.

8. THE NATIONAL LIBRARY OF MEDICINE, its regional branches, and other medical school libraries make available a number of data bases which contain bibliographic and other types of data on chemicals. The

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Chemical Abstract Service, for example, furnishes a bibliographic file and short abstracts of journal articles. A Chemical Abstracts Service Registry Number has been assigned to each compound and can be used to provide access to the Chemical Abstracts references listed in the data base.

Other computerized sources of information made available by the National Library of Medicine are the TDB (Toxicology Data Bank), TOXLINE, RTECS and CHEMLINE.

II. DATA ON SOURCES OF EXPOSURE:

Federal Sources

1. EPA: The EPA collects data on air and water pollution levels at sites throughout the United States. Its regional offices may have data available on effluent characteristics and air emissions of industries in the areas under their jurisdiction. The EPA can furnish data on those industries which have filed for smokestack or water discharge permits. Regional EPA offices may also have data on permits filed with state departments of conservation. Data can include plant name, location, SIC code, names of contaminants emitted, levels of emission, and limitations on emissions. Though a list of a plant's effluents and emissions is informative about the nature of environmental exposure, it will not correspond directly to the substances which workers are exposed to inside the plant.

The following is a list of programs or systems maintained by the EPA which may be useful in identifying potential study locations:

a) STORET (Storage and Retrieval of Water Quality and Related Data). Monitoring sites in virtually every U.S. county, this system furnishes data on levels of toxic industrial chemicals, metals and pesticides by site.

b) SAROAD (Storage and Retrieval of Aerometric Data). Monitoring stations in every major city and one-third of all U.S. counties provide data on levels of criteria pollutants by site and time.

c) NEDS (National Emissions Data). 78,000 point and area sources provide data on levels of criteria pollutants, emissions, and compliance by site and time since the early 1970's.

d) SOURCE TEST DATA SYSTEM. Provides data on stack emissions at specific point sources. Locations given.

e) RECRA (Resource Conservation and Recovery Act) Notification list: A list of all facilities in an EPA-administered region which handle chemicals in any way. Facility name, address, and the activity the facility is involved in (e.g., generation, disposal, treatment of chemicals and chemical wastes) are provided.

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2. NIOSH: NOHS (National Occupational Hazards Survey). This walk-through survey focused on chemicals that are considered substances of concern because of their mutagenic, teratogenic, or carcinogenic potential. The statistics generated give a conservative estimate of the numbers of workers exposed nationally to these compounds. The data can be accessed by chemical name and will output a list of SIC codes corresponding to the industries in which the substance is used.

3. OSHA: Under the Freedom of Information Act, copies of OSHA citations for violations of safety and health standards, summaries of occupational injuries and illnesses, and records of measurement and exposure to harmful substances can be made available by OSHA's regional offices.

State Sources

State offices for air emission and water discharge permits may be consulted to identify plants that emit toxic substances. Generally this source is less complete than the EPA's information.

State conservation agencies may also issue permits for use of pesticides and other controlled substances.

In a review of exposure data sources in New York and New Jersey done by the Sergievsky Center, it was found that the most useful source of information on potential exposure to industrial agents came from the Industrial Chemical Survey, published by the Department of Environmental Conservation of New York State. The Industrial Chemical Survey is an inventory of the use, manufacture, and handling of toxic or hazardous chemicals by specific industrial plants. The data on each plant include plant location and SIC code, a list of substances of concern, amounts of these substances used and on hand, their Chemical Abstract Service Registry numbers, method of waste disposal and discharge permits.

Departments of Conservation or Environmental Protection in other states may have similar inventories. For example, the New Jersey Department of Environmental Protection initiated an Industrial Survey Project last year to assemble a computerized data base on the uses and release into the environment of 155 chemicals. Like New York State's Industrial Chemical Survey it will inventory types and amounts of chemicals used by particular industrial plants, method of waste disposal, and plant location. It will also include numbers of employees in each facility. Data will be correlated with death and disease statistics in the state.

Other Sources

AFL-CIO: Its Workers' Institute for Safety and Health (WISH) in Washington, D.C. may be a source of informatin concerning chemical exposures in various industries.

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Local labor unions may be helpful in locating industries in which exposure to toxic substances has occurred for they often receive reports of illness in particular plants, exposure hazards, and violations of safety standards.

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Committees for Occupational Safety and Health (COSH) are organizations of union members and health activists that specifically investigate reports of occupational hazards to health and reproduction.

University Environmental Science programs: Researchers in Environmental Science departments may be studying exposures to industrial chemicals in their region and may have specific information on the type of exposure, how it is measured and how many people are exposed.

III. DATA ON EXPOSED INDUSTRIAL POPULATIONS

Federal Sources

NIOSH: NIOSH Industrial File: NIOSH acquired and modified the Dun and Bradstreet Market Identifier File consisting of 4,313,552 facility listings in the United States. The NIOSH Industrial File "exists in two versions, 1) in SIC sequential order, 2) on a county within State basis." Occupational information can be retrieved "for specific facilities within a designated industry or presented in aggregate form (e.g. total employees in an SIC.)"* Data provided include name of establishment, address, number of employees, total employees in the industry, and name of the chief executive.

Information from the Dun and Bradstreet Market Identifier File is also available from Dun and Bradstreet.

EPA: Facilities Index System: A list of industrial facilities in a region and number of employees in each. Information on chemicals used by each facility is slated for inclusion in the data base over the next year.

State-Level Sources

1. STATE INDUSTRIAL DIRECTORY: Privately published voluntary listing of manufacturers in a state. This marketing directory lists companies in alphabetical order, by county and community, by products and services and by SIC code. It provides the names of companies, addresses, number of employees, number of male and female workers in offices and in production, and the names of chief executives at each facility. The list of companies may not be complete. There may be missing data even for the companies included.

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2. STATE BUREAU OF THE CENSUS (DEPARTMENT OF COMMERCE) Census of Manufacturers: The census of manufacturers provides information by type of industry (SIC code) on the number of establishments with 20 employees or more, total number of employees, and total number of production workers. Figures are given for the state as a whole, for SMSA's (Standard Metropolitan Statistical Area), and selected counties and cities.

3. COUNTY BUSINESS PATTERNS: This directory lists types of industries found in each state by county. SIC code, number of employees in each type of industry, and number of establishments by employment size class are included.

4. ECONOMIC INFORMATION SERVICE (EIS) - Library file listing facility name, address, telephone number, volume of sales, and employment. Access to information is by four-digit SIC code.

5. DEPARTMENT OF LABOR: The New York State Department of Labor publishes an Employment Review which records number of firms by size classification and total number of employees in each firm-size classification for each industry in a state's labor market (an area corresponding almost exactly to the SMSA).

6. BUREAU OF LABOR MARKETING: Has information on the number of jobs per industry and number of women in manufacturing in each SMSA and non-SMSA county. Numbers of women are not listed by occupation, however.

Other Sources

1. CHAMBERS OF COMMERCE: A Chamber of Commerce may publish a manufacturer's directory for firms in its area. The Rochester area Chamber of Commerce, for example, publishes a list of manufacturers employing one hundred or more persons. Company names are listed alphabetically; addresses, telephone numbers, chief executive, products manufactured and number of employees per company are also included.

2. CENTRAL LABOR COUNCIL: This organization may be used to find out which industries in an area are unionized and what the names and locations of these unions are.

3. PLANTS: Plant managers and personnel departments may be questioned on the numbers of workers in each plant, breakdown by sex, number of workers in each area of manufacturing, etc. However, there may be some difficulty in eliciting information from plant management.

4. Hoar, Morrison, Cole and Silverman Occupation and Exposure Linkage System (for the study of occupational carcinogenisis): In order to identify the types of industries and occupations in which particular exposures may be found, it may be useful to consult Hoar et al.'s Occupation/Exposure Linkage System. The authors classified

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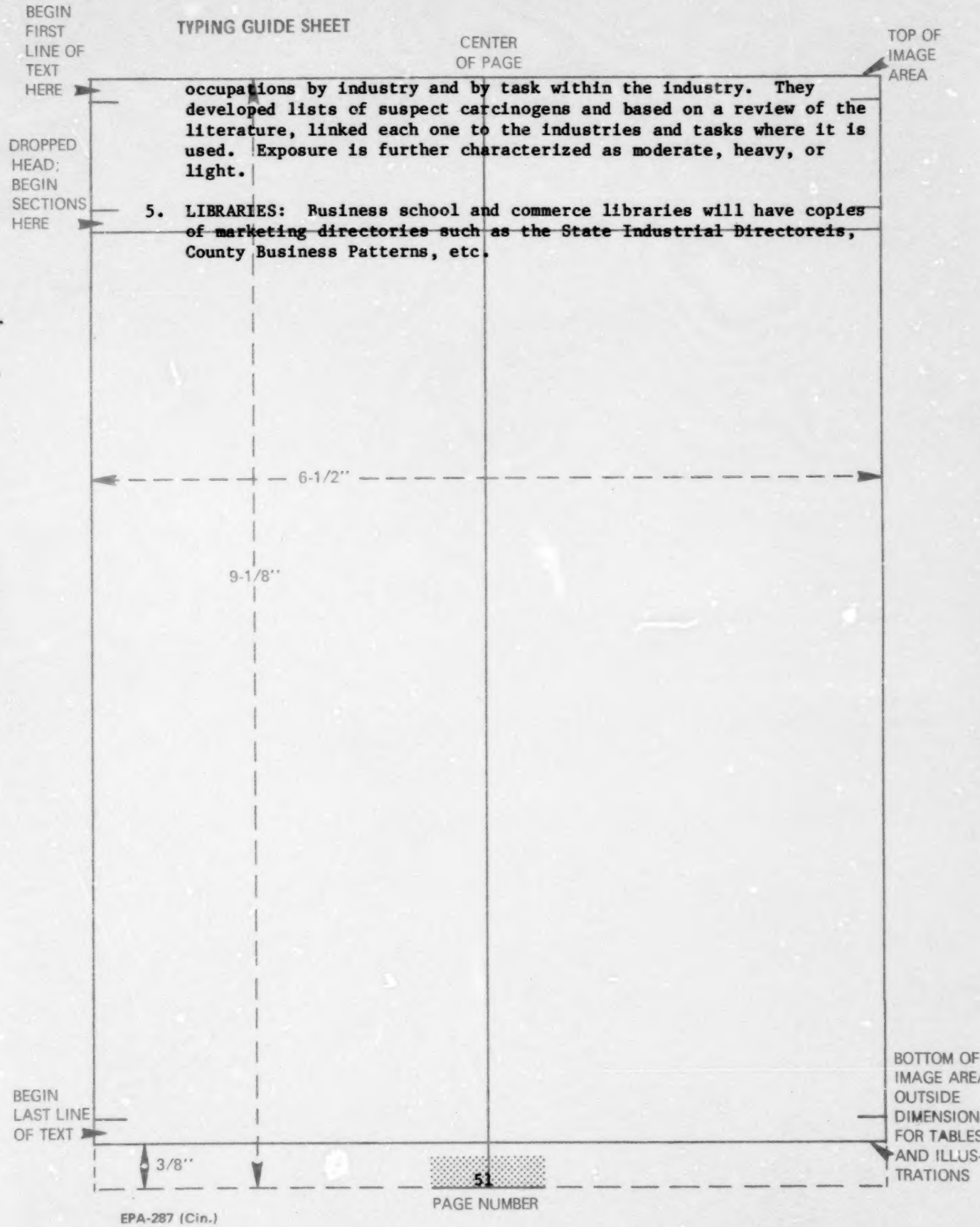
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occupations by industry and by task within the industry. They developed lists of suspect carcinogens and based on a review of the literature, linked each one to the industries and tasks where it is used. Exposure is further characterized as moderate, heavy, or light.
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5. LIBRARIES: Business school and commerce libraries will have copies of marketing directories such as the State Industrial Directoreis, County Business Patterns, etc.
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APPENDIX V

SOURCES OF DATA ON SPONTANEOUS ABORTION

I. VITAL CERTIFICATES

Vital statistics provide some information on fetal deaths, as well as livebirths, infant deaths, and outcomes such as birthweight and congenital anomalies. The data are available by state, county, and metropolitan areas, and can be obtained from the National Center for Health Statistics and state, county or city health departments.

However, vital statistics provide incomplete reports of fetal losses; in most states only those fetal deaths occurring at or after 20 weeks of gestation require certification. Few states (only nine in 1977, according to the National Center for Health Statistics) mandate reporting of all fetal losses, regardless of gestation.

Demographic data are also available on vital certificates, although the items recorded (e.g. occupation) may vary from state to state.

II. MEDICAL RECORDS

Hospital Records

Hospital records are another, potentially more complete, source of data on spontaneous abortions. In-patient records are sometimes computerized, and these data can usually be accessed by discharge diagnosis. Some hospitals have a Birth Registrar who maintains a special log of births and induced and spontaneous abortions that can facilitate data-gathering on these outcomes.

Physician Records

In communities where only a portion of women seeking medical attention for care of spontaneous abortions are admitted to hospital, physician records may provide more complete ascertainment of spontaneous abortion than hospital records. Potential disadvantages of this data source include: the necessity for manual record searches to identify subjects; the lack of uniformity in record-keeping from physician to physician; the potential for selection in the patient population (e.g. by social class, geographic area or level of obstetric risk). These same disadvantages may apply to hospital records as well.

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Use of either type of medical records for research on spontaneous abortion requires knowledge of medical service use patterns and obstetric care practices in the study area.

III. PERSONAL INTERVIEWS/QUESTIONNAIRES

Interview data potentially provide the most complete count of reproductive events, especially for outcomes such as early fetal loss where medical care may not have been sought.

Problems with this data source include: the possibility for bias in participation and/or reporting; possible misdiagnosis of the event by the respondent; potential interviewer bias.

IV. OTHER SOURCES

Prepaid Health Insurance Plan

Populations with prepaid insurance coverage (e.g. Kaiser-Permanente, HIP, HMO's) may seek prenatal care fairly early, thus increasing the likelihood that spontaneous abortion will be medically diagnosed when it occurs.

Special Registers

For example, the Perinatal Regional Network, a Robert Wood Johnson demonstration project in eight areas of the country, includes a computerized register of obstetric events; in some areas and for some time periods spontaneous abortions were among the events included.

Union/Employer Health Records

These represent a potential information source on worker populations. Records of employees/union members may contain health histories and insurance claims applications. However, available health benefits and patterns of use and reporting among employees would need to be ascertained before deciding on the quality of such data.

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9-1/8"

APPENDIX VI

OBSTETRIC RECORDS SURVEY QUESTIONNAIRE

M. Hatch and J. Kline

Reproductive Outcome Data

A. PHYSICIAN INTERVIEWS

Name _____

Address _____

Phone _____

Time and date of interview _____

For physicians practicing in a group, please note:

number of physicians in the practice _____

whether procedures and record are uniform _____

Period over which the office has done obstetrics _____

1. Ask for an estimate of the following data by month or by year, whichever the interviewee finds easier (for group practices, get totals for the group, not just for the physician interviewed):

total deliveries _____

total spontaneous abortions _____

seen in office _____

telephone report only _____

total spontaneous abortions hospitalized by this office _____

at what hospital(s) _____

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2. What proportion of obstetric cases in (name the area of interest) does this office handle?

3. Characteristics of obstetric population:

(a) patient residence

(b) race

(c) education

(d) age

(e) other demographic characteristics

6-1/2"

4. Ask for estimate of the proportion of women in (name area of interest) with (a) livebirths and (b) spontaneous abortions who do not attend a hospital, physician, or other medical facility for care. (We need to gauge what proportion of reproductive events could not be either ascertained or validated in physician or hospital records.)

4a. What is the basis for this estimate?

5. How soon after their last menstrual period do patients usually come in for confirmation of pregnancy? (NOTE: IF physician gives a broad range, ask what percent comes in at the early end and what proportion toward the end of the range. The purpose of the question is to find out how many first trimester abortions may not be medically attended.)

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5a. What proportion are confirmed by pregnancy test? What proportion by physical exam?

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5b. Where pregnancy tests have been used, ascertain:

type of pregnancy test _____

where results are analyzed _____

where results are recorded _____

6. What proportion of patients experiencing spontanous abortion have had their pregnancy confirmed before the abortion?

6-1/2"

6a. Of that proportion, how many by pregnancy tests? How many by PE?

9-1/8"

7. What is the office protocol with respect to a spontaneous abortion when:

(a) patient gives self-report by phone, pregnancy unconfirmed prior to phone call.

(b) patient phones in self-report, pregnancy has been confirmed prior to phone call.

Is the phone contact recorded in the chart? Is date of abortion recorded? Is LMP recorded? What other data are recorded?

Is a patient visit always or sometimes required following report of a spontaneous abortion?

What proportion of patients reporting spontaneous abortion are hospitalized? and for what reasons?

Are pathologic examinations done on the products of conception to confirm pregnancy? When and where?

Pregnancy unconfirmed

Pregnancy confirmed

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8. Hand the interviewee the sheet with the list of variables (checklist of variables) and have him/her fill it out.

9. How many total charts does this office have? _____

How are they filed and stored? _____

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10. In this office, is there any way to pull only those charts of women who have had pregnancies--e.g., an ongoing list of OB patients; list of those pregnancy tested; list of path exams on POC; etc.

11. Within the chart, is there any quick way to retrieve all data on pregnancies?

12. Would he/she agree to a record search if a study were to be undertaken?

13. Ask whether doctor would be willing to provide us access to names of patients for the purpose of linking across facilities (We would of course respect confidentiality of patients.)

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14. FOR ALL INTERVIEWEES: Ask to review 2-5 randomly selected charts. (In case of group practice, ask for two charts per physician.)

(a) check especially for information on smoking, alcohol, residence, occupation.

(b) note whether chart:

i. is typed or handwritten; if latter, is it legible?

8-1/2"

ii. does or does not have a facesheet?

iii. is organized from current to past, or vice versa?

iv. provides a continuous history or has separate chart for each calendar year?

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(c) in case of GP, is reproductive data difficult to cull from record?

Comments:

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Checklist of Variables

Interviewee _____

Address _____

Phone _____

For the following variables, please estimate what proportion of your records contain this information:

	a) for a live or still birth	b) for a spontaneous abortion
	DATE OF LMP	
	DATE OF ABORTION OR BIRTH	
	OTHER ESTIMATES OF GESTATION (e.g. intrauterine size)	
	MOTHER'S DATE OF BIRTH	
	FATHER'S DATE OF BIRTH	
	MOTHER'S PREVIOUS REPRODUCTIVE HISTORY	
	RACE OF MOTHER	
	RACE OF FATHER	
	EDUCATION OF MOTHER	
	EDUCATION OF FATHER	
	OCCUPATION OF FATHER	
	OCCUPATION OF MOTHER	
	PREGNANCY TEST RESULTS	
	PATHOLOGICAL REPORT ON PRODUCT OF ABORTION	
	ZIP CODE OR OTHER INDICATOR OF PATIENT ADDRESS	

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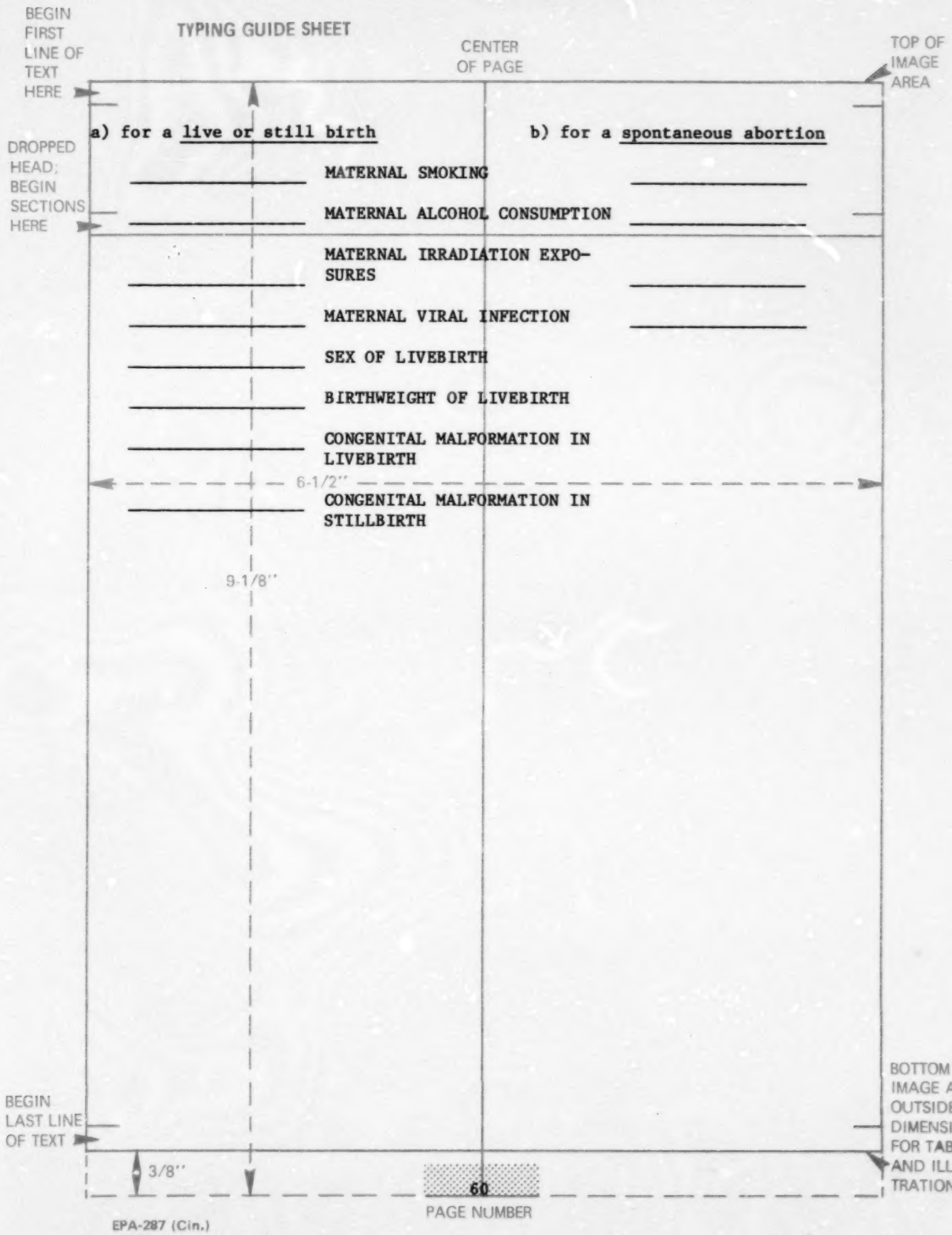
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a) for a live or still birth
b) for a spontaneous abortion
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MATERNAL SMOKING
MATERNAL ALCOHOL CONSUMPTION
MATERNAL IRRADIATION EXPOSURES
MATERNAL VIRAL INFECTION
SEX OF LIVEBIRTH
BIRTHWEIGHT OF LIVEBIRTH
CONGENITAL MALFORMATION IN LIVEBIRTH
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CONGENITAL MALFORMATION IN STILLBIRTH
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Reproductive Outcome Data

B. HOSPITAL INTERVIEWS

Name _____

Address _____

Phone _____

Time and date of interview _____

Name of hospital _____

Number of beds total _____

Number of OB beds _____

Number of physicians admitting OB/GYN patients _____

1. **Ask for an estimate of the following data by month or year, whichever the interviewee finds easier:**

   total deliveries _____

   total spontaneous abortions _____

   Inpatients _____

   Outpatients _____

   Clinics _____

   ER _____

   total induced abortions _____

2. **Does this hospital have a "Birth Registrar"--someone who keeps summary data on births, stillbirths, induced and spontaneous abortions?**

3. **Are fetal death certificates filled out in hospital? Beginning at what gestation?**

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4. Please characterize your OB population in terms of:

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(a) residence

(b) race

(c) education

(d) age

(e) other demographic characteristics

5. Please estimate the proportion of women in the area with (a) livebirths and (b) spontaneous abortions who do not attend a hospital, go to a physician, or to another facility for care. (We need to gauge what proportion of reproductive events could not be either ascertained or validated in physician or hospital records.)

5a. What is the basis for this estimate?

9-1/8"

6. Are most patients with livebirths or spontaneous abortions admitted through a private physician, or do some patients have no physician?

7. a. How are charts filed--by name, unit number, admitting or discharge diagnosis? Is it possible to access charts by diagnosis?

b. Are the records computerized?

If so, are outpatient records computerized as well?

What data are entered onto the computer?

8. How would one identify every spontaneous abortion that occurred at your hospital? IF RECORDS ARE COMPUTERIZED: Have you ever checked whether your computer records pick up every case from the admissions book, path log, OB clinic log, etc.?

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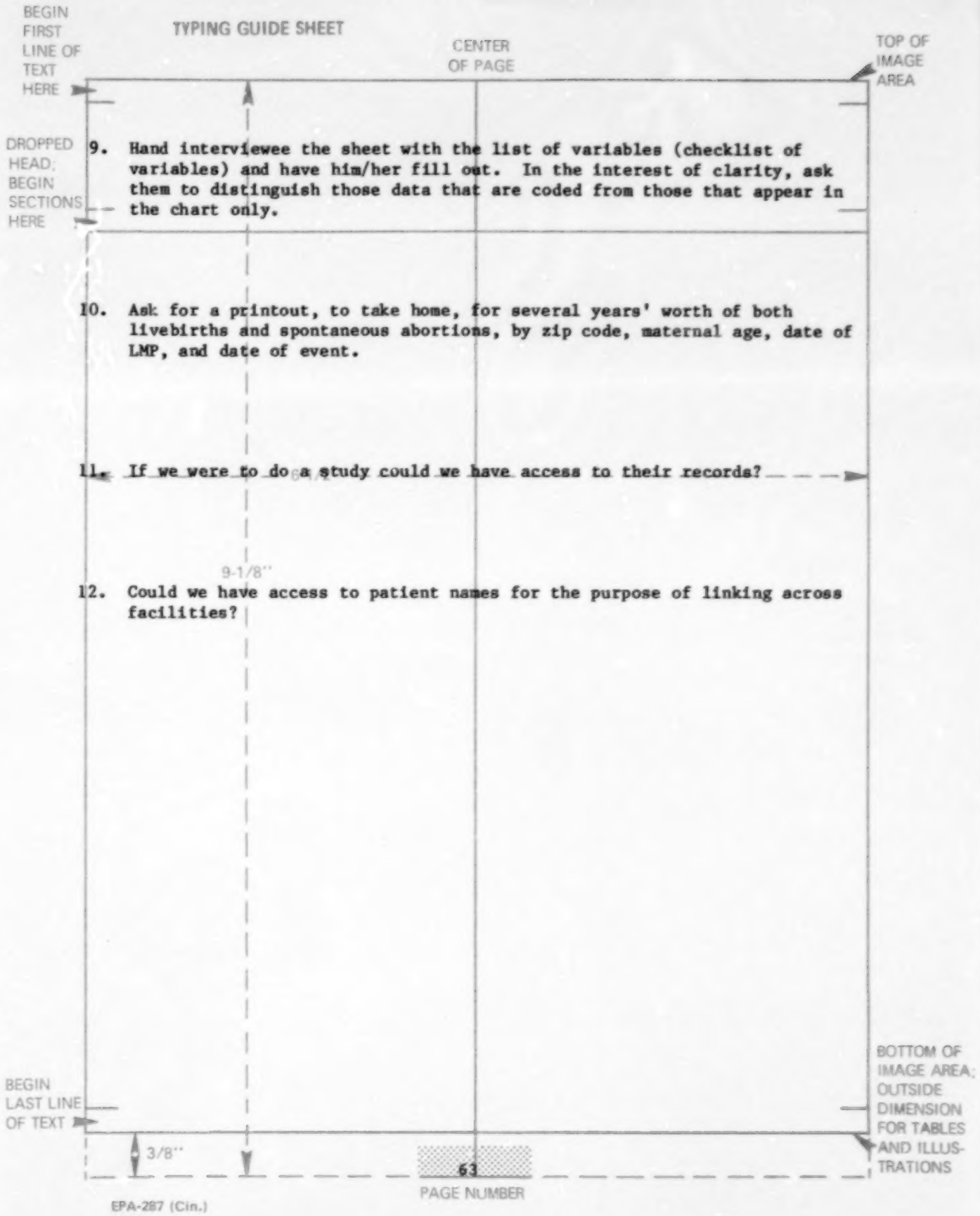
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9. Hand interviewee the sheet with the list of variables (checklist of variables) and have him/her fill out. In the interest of clarity, ask them to distinguish those data that are coded from those that appear in the chart only.
10. Ask for a printout, to take home, for several years' worth of both livebirths and spontaneous abortions, by zip code, maternal age, date of LMP, and date of event.
11. If we were to do a study could we have access to their records?
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12. Could we have access to patient names for the purpose of linking across facilities?
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APPENDIX VII

REFERENCES FOR PUBLISHED AND/OR PRESENTED PAPERS RESULTING FROM THIS PROJECT

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